REPORT OF THE HOSPITAL

OCTOBER 15, 1920

ANNUAL REPORT OF THE WORK OF THE HOSPITAL

In the absence of Doctor Cole, who has been on leave of absence since January, the following report has been prepared with the collaboration of the other members of the Hospital Staff.

The prophecy of Doctor Cole in the last annual report that "men are still ready to undertake quietly the study of disease" has been fully justified. The effects of the war upon the spirit of research have been largely eliminated, and the various members of the Hospital Staff have renewed their efforts with the spirit instilled by Doctor Cole in former years.

It is now ten years since the opening of the Hospital. A review of the work done here during the past decade would seem to justify the effort and money expended. But far greater results have been accomplished than can be estimated in the number of papers published, or the total patients treated. Men have been trained in the combined bedside and laboratory investigation of disease; a model hospital for this purpose has been developed. What seemed a dream to those of us who were privileged to be present during the early years has become a reality. Then there was no such place to work, and but few men looked forward to a career in clinical investigation; now many of our University Medical Schools are modeling their medical clinics along lines laid down in this Hospital and are offering positions to men trained here, and many young men are

seeking opportunities both here and in these clinics. It is a great pleasure to be able to acknowledge our indebtedness to our Director who has so clearly shown the way and to all those in authority who have made the work materially possible.

The problems continued from previous years have been pneumonia and cardiac disease; three new lines of investigation covering nephritis, measles, and acute rheumatic fever have been started. The progress in each of these problems is covered under the reports of each of the members of the Staff.

Dr Swift

The investigation of acute rheumatic fever has been undertaken with Doctor Boots; Doctor Miller will also collaborate in this problem during the coming year. During the past year there have been an unusually small number of cases of acute rheumatic fever in the various hospitals in New York. We have therefore had only a few cases of the disease for study in our wards. Blood cultures and cultures of fluid obtained from the joints with ordinary aerobic methods and special anaerobic methods have been made with negative results; these results are in agreement with those previously obtained by one of us. Attempts have also been made to find antibodies to various types of non-hemolytic streptococci in the blood serum of these patients during the course of the disease; so far no antibodies have been demonstrated with the methods used. While these observations should be extended in order to be conclusive, it seems more and more probable that streptococci play a minor or secondary role in the production of rheumatic

fever. As a direct corollary to this problem it was shown that the injection of both living and killed streptococci into the joints of rabbits is followed by the appearance of antibodies in the blood serum; these immune bodies are formed as quickly as if the bacteria are injected into the blood stream, and more rapidly than if they are introduced subcutaneously or intraperitoneally.

A new line of investigation has been started: Attempts are being made to produce some or all of the symptoms of the disease in laboratory animals by inoculating them with the blood and joint exudate, and filtered throat washings obtained from patients during the various stages of the disease. A large number of rabbits and guinea pigs have been studied; in some instances distinct arthritis has resulted, in others lesions of slighter degree have been observed. During the coming months the material from these animals will be subjected to microscopic study by Doctor Miller as the final criteria must be based on studies of this type.

A general study of the effect of salicylates upon the formation of antibodies has been undertaken. The salicylates are the chief drugs used for the alleviation of the unpleasant symptoms of rheumatism, but little is known as to their mode of action. In our experiments it was found that there was somewhat slower rate of antibody formation as well as smaller amounts of antibody in inoculated animals receiving sodium salicylate than in controls; this was especially marked when the amount of antigen injected was small in amount.

A method for the preservation of stock cultures of bacteria by drying them in the frozen state has been so simplified that it is applicable in any laboratory. With proper technique bacteria may be preserved in this manner for several years. The dangers of contamination and change in virulence and loss of other properties incident upon frequent transfers of cultures can thus be largely obviated. Bacteria kept in this form are much easier to ship. It is hoped the method will have wide application in various laboratories.

Dr Avery and Dr Cullen

During the past year Dr Avery and Dr Cullen have been engaged in the study of the biochemistry of the intracellular substances of pneumococcus. Methods have been devised for obtaining active solutions of cell bodies of the bacteria with little or no resultant change in their antigenic or chemical nature; a technique has been developed for studying the biologic activity of these intracellular substances apart from the living organism with which they are so intimately associated. Since most metabolic processes of the living cell are brought about by the action of enzymes the attempt was first made to determine whether or not the intracellular substances recovered from pneumococci possessed enzyme action. By testing these cell-free solutions on suitable substrates enzymes have been readily demonstrable. These enzymes have been found to possess the power of actively hydrolyzing peptones into simpler peptides and amino acids; of converting carbohydrates into simpler products, and of splitting esters into fatty acids. Evidence has been presented that these enzymes exist preformed within the bacterial cell and are therefore of the nature of endoenzymes. In other words it has been possible by means of sterile extracts of pneumococci to correlate many of the functional activities of the living bacterial cell with the enzymotic processes of the intracellular substances when removed from the growing organism. Further, it has been shown that the optimal zone of hydrogen ion concentration within which these enzymes are active bears a striking relationship to the reaction range which limits the

biologic activities of the living organism itself.

Since the last report three papers dealing with the nature and action of the intracellular enzymes of pneumococcus have been accepted for publication and are now in press:

Studies on the Intracellular Substances of Pneumococcus

1. The proteolytic enzymes.

2. The lipolytic enzymes.

3. The carbohydrate-splitting enzymes.

Continued studies on the nature of the intracellular substances of pneumococcus have further demonstrated the existence within the bacterial cell of an enzyme or group of enzymes which are bacteriolytic in nature. Minimal amounts of an active enzyme-containing solution of pneumococcus when added to a substrate of dead pneumococci of the same or different type cause rapid and complete dissolution of the bacterial bodies. This bacteriolytic enzyme has been found, however, to be specific for the species, in that it is without effect when allowed to act under similar conditions on the dead cells of closely allied organisms such as staphylococcus aureus and streptococcus hemolyticus.

Moreover, in addition to the enzymes described, sterile solutions of the intracellular substances of pneumococcus have been found to contain other active agents which manifest their specific nature when allowed to act on blood. These in brief are first the endohemolysin which causes solution of the red corpuscles, and secondly, a substance which is able to transform hemoglobin into methemoglobin. The hemolytic substance is in nature an endohemotoxin, which is able to exert its

action only after its release from the cell by disintegration of the bacterial body. This hemolysin, previously considered one of the most labile of the substances of bacterial origin, has been found to maintain its activity over a period of several weeks when obtained by the methods described. The nature of the reactive substance of pneumococcus which induces the formation of methemoglobin has been investigated by several workers. Considerable variance of opinion exists as to whether the formation of methemoglobin occurs only as the result of the action of the living pneumococcus on blood, or whether a similar transformation of hemoglobin can be induced by bacterial extracts and culture filtrates. The results of work already done establish the fact that active enzyme-containing solutions of pneumococci in which no living organisms are present are able under proper conditions to produce methemoglobin. The nature of the mechanism of this reaction is being investigated further.

It is felt that these studies on the biochemistry of the intracellular substances of pneumococcus are important, not only theoretically because of the added knowledge gained concerning the life processes of the organism, but also clinically because of their significance in the interpretation of certain of the blood changes which occur in pneumococcal infections in man.

Dr E. G. Stillman

Doctor E. G. Stillman and Miss Bourn have made an extensive biological study of the hemophilic bacilli. The small Gram negative hemophilic bacilli which have gradually come to be considered as belonging to one group of organisms and to which the name B. influenzae has been given, appear in the light of the present study to be rather a group of closely allied bacilli which have demonstrable biologic differences. The bacillus which Pfeiffer first described and associated with clinical influenza is now questioned as being the etiological factor in the spread of the disease. However, the percentage of cases in which the bacillus of Pfeiffer has been recovered is great enough to indicate that this organism may be at least a secondary invader. Since the first description of this hemophilic bacillus in 1892 by Pfeiffer, little has been added to our knowledge of its biological characteristics.

In this study it has been found that the hemophilic bacilli observed divide themselves naturally into two large groups according to their ability to hemolyze whole blood. The hemolytic group comprises those organisms originally described as Bacillus X by Pritchett and Stillman, and occurs in normal mouths.

Both the non-hemolytic and hemolytic group of hemophilic bacilli attain a final hydrogen ion concentration of approximately pH 6.4 although the hemolytic group may reach pH 5.8. Both produce acid in dextrose, but in both groups only certain strains ferment saccharose. The greater ability

of the hemolytic organisms to ferment sugars may be a basis for further differentiation.

A tentative classification defines a small subgroup of the hemolytic group formed by those strains which produce indol and gas but do not ferment saccharose. These strains appear to ferment sugars less readily and require further study to determine whether the indol-producing strains are also gas producers. The greater number of the hemolytic strains, however, do not produce indol or gas, but ferment saccharose.

The non-hemolytic organisms are subdivided into two fairly even groups comprising indol-producing and non-indol-producing strains. None of the indol producers form gas in contrast with the hemolytic group. With one exception, the non-hemolytic indol-producing strains all ferment saccharose. A large majority of the non-indol-producing organisms of the non-hemolytic type do not form gas and do not ferment saccharose. The indol-negative strains which do form gas, with a single exception, all ferment saccharose.

The classification made in this study is merely a tentative one. Undoubtedly when the technique of these reactions is more nearly perfected and a larger number of hemophilic bacilli have been studied, the group differentiations will be more striking and regular.

Although the number of strains of B. influenzae employed in this study is too small to warrant any definite conclusions, it would seem that the non-hemolytic bacilli isolated from persons suffering with and recovering from respiratory infections and those isolated from normal mouths during

the epidemic period show certain biological differences from those strains recovered from normal persons during the winter of 1919 to 1920. The group of non-hemolytic hemophilic bacilli recovered from normal mouths during the winter of 1919 to 1920 show a higher percentage of strains which ferment the polysaccharides, maltose, saccharose and dextrin; more strains which produce gas, but fewer indol-producing strains.

Doctor O. H. Robertson, who is now on his way to China to assume his duties in the Department of Medicine of the Peking Union Medical College, during the past year acted as voluntary assistant on the Hospital Staff in the clinical and laboratory work on pneumonia. During the winter Doctor Robertson completed a study with Doctor Kligler which was begun the previous summer "On the cultivation and biological characteristics of Spirochaete obermeieri (recurrentis)".

In a publication last year by Lowe, Hierschfeld and Wallach of Mt. Sinai Hospital, a test was described for determining the type of pneumococcus in pneumonia by means of a blood reaction. The test briefly consists in determining the relative rates at which the three types of pneumococci produce methemoglobin in the laked blood of the infected individual. The type organism which first produces methemoglobin in the laked blood is considered to be the same type as that producing the disease. Careful and accurate observations on the validity of this reaction by Doctor Robertson failed to substantiate the reliability of the test as a diagnostic procedure.

Doctor Lyon, whose military assignment to the Hospital during the war eventually led to his official appointment to the Hospital Staff as Assistant Resident Physician, has resigned to assume the practise of medicine in Boston. During the past winter Doctor Lyon studied the antigenic relationship of a large series of strains of B. influenzae in an attempt to determine whether or not specific differences exist among the hemophilic bacilli. The recognition of biological relationships existing between varieties of this species of bacterium would contribute much to the development of knowledge of the significance of these organisms in respiratory disease. Doctor Lyon's report, however, indicates that this group of organisms shows great diversity and heterogeneity as far as antigenic characters are concerned.

Dr Blake: Studies on Pneumonia.

In completion of work previously conducted at the Army Medical School in Washington, D. C., a detailed study of the histological pathology of pneumonia produced in monkeys by intratracheal injections of pneumococcus, of Streptococcus hemolyticus, and of Bacillus influenzae has been carried out and an attempt has been made to work out the pathogenesis of the different types of pneumonia caused by these three organisms.

Study of the pathology of pneumococcus pneumonia in monkeys has shown that it is essentially the same as that of pneumococcus lobar pneumonia in man. It has been shown that in monkeys the pneumococcus invades the lung near the hilum

and spreads through the tissue by way of the interstitial framework and lymphatics and that consolidation begins centrally and spreads toward the periphery of the lung.

Similarly it has been found that the pathology of hemolytic streptococcus pneumonia in monkeys corresponds to that of streptococcus interstitial and lobular pneumonia in man. The streptococcus invades the lung by the same paths as the pneumococcus but the end result is different because of a different tissue response to the infection and a different effect of the organism on the tissue.

Bacillus influenzae likewise produces a distinctive type of bronchopneumonia in monkeys similar to that produced by B. influenzae in man. The injection in this case primarily affects the mucous membranes of the bronchial tree with adjacent areas of peribronchial consolidation.

Dr Blake and Dr Trask: Studies on Measles.

By the intratracheal injection into monkeys of unfiltered nasopharyngeal washings from cases of measles a relatively constant group of symptoms has been induced which closely resembles those of measles in man. Of 8 monkeys inoculated with unfiltered washings 6 came down with this group of symptoms. The same reaction has been induced in two monkeys by the intratracheal injection of filtered (Berkefeld N) washings from two cases of measles. Cultures of these washings showed no growth after two weeks incubation.

The symptoms and signs induced have been constant and definite in character: After an incubation period of 6 to 10 days the inoculated animal becomes listless and drowsy,

the conjunctivae become injected, and small discrete red spots appear on the labial mucous membranes. These spots increase in number and may eventually coalesce in the course of 2 to 4 days to form a diffuse red granular rash. This rash is usually limited to the labial mucous membranes but may extend to the inside of the cheeks. It is never present on the roof of the mouth, soft palate or tongue. The individual macules may or may not show the minute bluish white centre characteristic of Koplik spots. One to four days after the onset an eruption of small discrete red maculopapules appears on the skin, usually coming out first on the face. The rash rapidly increases in the number and size of the individual lesions and may in the course of 2 to 3 days extend to the skin of the shoulders, upper arms, chest, abdomen and thighs. The rash is constant in character but varies considerably in extent in different animals. By the time the exanthem is fully developed the rash on the mucous membranes has begun to fade and soon disappears. The exanthem in turn rapidly fades, sometimes with a bran~~n~~y desquamation, sometimes without. By the 6th to the 10th day after onset depending upon the severity and the extent of the reaction, all symptoms have disappeared and the animal again appears well. Coincident with this group of symptoms there is a constant and definite fall in the total leucocyte count, frequently constituting a true leucopenia. Symptoms of rhinitis and bronchitis do not occur. Histological sections of the lesions of the skin and mucous membranes show the characteristic picture of the corresponding lesions of measles in man. Cultures of the blood made

both during the incubation period and during the course of the reaction in a variety of media, aerobic and anaerobic, have consistently shown no growth.

The characteristic reaction which follows the inoculation of monkeys with the nasopharyngeal washings of measles patients has been successfully transmitted from monkey to monkey through six passages by the intratracheal inoculation of saline emulsions of the skin and mucous membranes of monkeys killed shortly after the appearance of the exanthem. From the 4th passage monkey it was also successfully transmitted to three monkeys by means of citrated blood injected intravenously. This experiment showed the blood to be capable of transmitting the reaction from at least the 7th to the 13th day after intratracheal inoculation of the donor monkey. The reaction has furthermore been transmitted through 2 passages by inoculation of nasopharyngeal washings of monkeys in the early period of the reaction. The character of the reaction in the passage monkeys was identical with that which occurred in monkeys inoculated with nasopharyngeal washings of patients.

The evidence obtained is believed to be sufficient to warrant the conclusion that the reaction is caused by the virus of measles.

Dr Cohn

During the past year the studies on the action of digitalis were continued with Doctor Levy. In patients, the action of digitalis by mouth was compared with the action of G-strophanthin injected intravenously. It was found, in brief,

that an effect with digitalis may occur in a little more than two hours. After giving strophanthin the effect may be seen in 20 minutes or less; with digitalis the effect on the rate of the ventricles (when the auricles are fibrillating) long outlasts that of strophanthin in the ratio of about 15 to 3 days. On the T-wave of the electrocardiogram strophanthin has a slight effect or none at all. To establish these observations satisfactorily and to amplify them, it is proposed to continue this study this year. The data serve as the basis for part of the general study of the action of digitalis on each of several varieties of the diseased heart, e.g. when normal mechanism is present, when the auricles fibrillate, when hypertensive arterial disease is involved.

In animals, the attempt was made to ascertain whether the change in the T-wave of the electrocardiogram which occurs on giving digitalis to patients is associated with a beneficial action. Our primary object, to show that an improvement in contraction takes place when the T-wave changes, was attained. But the results were unsatisfactory in so far that they were obtained after severe operative procedures, and under anesthesia. The spring was therefore occupied with preparing dogs after the method of van Leersum.

The van Leersum method consists in placing the common carotid artery in a situation always accessible, so that blood pressure readings may be made of it whenever desirable. This is accomplished by an aseptic operation. Two incisions of the skin are made, parallel to each other

and to the artery itself. The skin flap is freed and its edges are sewed so as to include the artery in a tunnel. The artery so prepared is now available for blood pressure determinations by the usual means employed in man. We expect to make much use of animals so prepared in the study of drugs, for the present especially of the digitalis series.

In a series of about 15 patients suffering from pneumonia teleroentgenograms were made by Doctor Levy at frequent intervals during the acute stage of the disease and during convalescence in order to ascertain changes in the size of the heart. A few of these series of plates only have been measured. It appears from the data so far available that the method is a satisfactory one for this purpose. In certain instances an alteration in the size of the heart occurs in the acute stage of both lobar and bronchopneumonia. This work will be continued during this winter and should be materially facilitated by use of the bedside x-ray apparatus.

Doctor Binger has continued his study of the lung volumes in patients suffering from heart disease. His results are more fully covered elsewhere.

Doctor Raisbeck, of the Flower Hospital, is pursuing the very useful and laborious work of measuring the electrocardiograms of normal men (about 160). The work requires much time on account of the great attention to detail necessary to devote to it. Under the circumstances, its completion will probably be delayed for some time. When complete, very accurate and satisfactory data of the limits of the normal electrocardiogram will be available.

Doctor Levy and Doctor Cullen, in making biologic assays of several lots of a commercial preparation of G-strophanthin prior to administering it to patients, found wide variations in potency. Experiments were undertaken to ascertain the cause of the deterioration and to devise a method for preparing a stable solution of the drug for therapeutic purposes.

It was found that many of the glass containers commonly used in the laboratory and most of the glass ampules employed in marketing sterile solutions for hypodermic or intravenous medication yield sufficient alkali, on autoclaving, to change appreciably the reaction of distilled water toward the alkaline side. This increase in alkalinity is sufficient to render biologically inert and partially to decompose aqueous solutions of crystalline strophanthin in the concentration ordinarily employed in the clinic.

For clinical use, therefore, they found that crystalline strophanthin should be dissolved in a buffer solution (0.02 M standard phosphate solution at pH 7.0 is satisfactory) and marketed in hard glass ampules, thereby insuring stability of reaction with preservation of biologic activity.

Dr Van Slyke

With Doctor Stadie the work on improvement and revision of the methods for determining the blood gases has been finished and prepared for publication. With the experience that has been gained it is probable that these methods are now fairly well standardized in permanent form. The

methods revised in more or less degree include those for the determination of oxygen, hemoglobin, methemoglobin, carbon dioxide, nitrogen gas and carbon monoxide. Also the technique has been so developed that it is possible to determine all the gases on a single 1 cc. sample of blood.

Doctor Stadie and Doctor Binger are engaged in a study of the respiration in pneumonia and in cardiac disease, and in a study of the physiological and therapeutic effects of oxygen administration. For the latter work they have constructed an "oxygen chamber" capable of holding a patient and nurse, and of having its oxygen content kept at any desired level. The preliminary experiments on cyanotic cardiac and pneumonia patients have yielded apparently striking results in change of oxygen saturation of the blood, character of respiration, and pulse rate, but as the work is still in the preliminary stage and requires for its confirmation more extensive observations, it will be carried out during the coming year.

Doctor Binger is continuing his work on respiratory factors in heart disease. During the spring and summer he has been engaged in modifying the lung volume method of Lundsgaard and Van Slyke in such a manner that it can be used with patients who are acutely ill. In the original method, the subject, by 4 or 5 vigorous respirations to and from a bag containing 2 liters of oxygen, completely mixed the air in his lungs with the oxygen in the bag. The volume of air in the lungs (lung volume) was calculated from the composition of the gas mixture obtained. The difficulty in applying the method

to ill patients lay in their inability to breathe deeply. With the ordinary respirations of which they are capable, several minutes instead of a fraction of a minute are required to completely mix the gases, and in this time so much carbon dioxide develops that it causes dyspnea. The difficulty has been met by inserting between the mouth-piece of the apparatus and the oxygen bag, a bottle containing glass beads moistened with KOH solution. This removes the CO_2 so that it is possible for the subject to breathe as long as may be necessary without distress. When the final gas analyses are made, the CO_2 absorbed by the alkali is estimated by rinsing off the beads, and determining the CO_2 content of the wash water by means of the apparatus originally designed in this laboratory for CO_2 determination in the blood.

The problem to be attacked with this method is the question of the lung volume changes in heart disease. Peabody has shown that the vital capacity is reduced, and that the reduction is more or less in proportion to the severity of the cardiac condition. It remains to be found whether the loss in vital capacity is due (1) to inability to fill the lungs to a normal total volume; (2) to a large residual air leaving relatively little room for expansion, even though total capacity is undiminished, or (3) to an obliteration of part of the effective lung area, in which case it would be expected that residual air and vital capacity would show a parallel reduction. Interesting preliminary results have been obtained, but too few in number to warrant conclusions.

During his experiments with the method Doctor Binger made the discovery that during the breathing of the oxygen-air mixture, oxygen was absorbed from the lungs at a very much greater rate than when air of only normal oxygen content was breathed. The respiratory quotient also became abnormal, the oxygen absorption being out of all proportion to the CO_2 evolution. The question was raised, whether this accelerated oxygen consumption is due to physical solution of oxygen at higher tension in the body fluids, or to an actual acceleration of metabolic oxidation in the body. This question is also under investigation. Its answer may assist in explaining the therapeutic effect of oxygen in heart disease and pneumonia.

With Doctor Austin and Doctor Cullen a study has been begun of the blood changes in ether anesthesia, the problem being a continuation of our work on the general subject of acidosis. It is found that during light ether anesthesia the bicarbonate content of the arterial blood falls, the carbon dioxide tension (determined directly in the blood by the tonometric method) rises, and the hydrogen ion concentration increases. These phenomena indicate a state of uncompensated acidosis,- the alkaline reserve is diminished, and the actual reaction (hydrogen ion concentration) shifts heavily towards the acid side. The oxygen saturation of the arterial blood may be increased in light anesthesia, indicating an increased ventilation. The latter is not, however, sufficient to keep the CO_2 tension and hydrogen ion concentration of the blood

within normal limits, as it would be kept if the respiration gave a normally great response to the CO_2 stimulus. It appears, therefore, that even in light ether anesthesia the respiratory center, though not entirely unresponsive to stimulus, is markedly deadened.

In deep ether anesthesia the carbon dioxide tension in the arterial blood rises still higher, and may reach double the normal. Hydrogen ion concentration becomes still greater. Respiration not only fails to respond fully to the CO_2 stimulus, but is in fact retarded to such an extent that the oxygen saturation in the arterial blood may fall below that normally found in venous blood. The blood also tends to become concentrated.

Conductivity and chloride determinations in the serum indicate only minute changes. The only striking electrolytic changes appear to be the increase in hydrogen ions and replacement of part of the bicarbonate HCO_3 ions by anions of acids as yet unidentified.

The entire picture indicates that even the initial stages of ether anesthesia involve a deadening of the respiratory center, or a loss of respiratory efficiency, sufficient to permit the blood reaction to shift markedly towards the acid side. The condition steadily progresses, as anesthesia deepens, until ventilation becomes so inefficient that oxygenation also fails. Accompanying these changes is a progressive fall in the alkaline reserve.

The results suggest caution in following Y. Henderson's plan of supplying air containing 5 or more per cent of

CO_2 to patients under ether, in order to prevent loss of carbonic acid (acapnia). They actually have an accumulation of it. It may be that oxygen lack is a more important factor than CO_2 retention and the accompanying acidosis. In that case still further increasing the CO_2 retention by breathing CO_2 might whip up the partly deadened respiratory center and improve oxygenation of the blood. If the acidosis also is an important factor in the injury that may be done by the anesthetic, however, increasing it by breathing CO_2 would increase the danger. It appears that the two factors require separate study.

Doctor Austin, Doctor Edgar Stillman and Doctor Van Slyke in the study of nephritis experienced trouble at the start in applying the Ambard formula to estimate the urea-secreting power of the kidneys. They consequently directed their attention to this point for the time, and experiments on animals, normal men, and patients, led to the following conclusions: (1) Ambard and his collaborators, presumably because of the inaccurate (hypobromite) method used in their urea determinations, were in error in finding that the rate of urea excretion rises as the square of the blood urea concentration. As a matter of fact it rises in simple direct proportion to it, i.e., doubling the blood urea does not quadruple the output, as assumed in the Ambard equation, but merely doubles the output. (2) The relationship between concentration of urea in urine and rate of urea excretion assumed by Ambard holds so loosely that it is often difficult to ascertain any relation at all.

This work has led to the development of a new formula for expressing the urea-secreting efficiency of the kidneys, based on the facts that the excretion rate is proportional, first to the blood urea concentration, and second to the square root of the urine volume. Further work has been done in accumulating data to test the accuracy of the formula in normal individuals, the limits of normal variation in the results obtained with it, and the consistency of deviations from the normal obtained in nephritis.

Miss Hiller in her work on protein analysis last spring encountered in gelatin a nitrogenous substance in the hexone base portion which did not appear to be any of the known amino acids. It is possibly an intermediate peptide difficult of hydrolysis by acids, but it is also possible that a clue has been found leading to the discovery of a hitherto unknown amino acid. It was not present in the proteins examined other than gelatin. It gives the pyrrol reaction and is difficult to crystallize in any form yet tried except the phosphotungstate. Work is being pushed to identify the substance.

As a result of a consultation with Professor L. J. Henderson of Harvard a joint piece of work was decided upon involving Henderson, McLean, who was at that time with Henderson, but is now here, and some of the men in this laboratory. The object of the research is to establish the laws which govern the reciprocal effects in the blood of oxygen and carbon dioxide tensions, and the migration of electrolytes between the blood cells and the plasma under the changing gas

tensions. It has been shown by Haldane that, in Henderson's words "Oxygen pushes carbon dioxide out of the blood, and carbon dioxide pushes oxygen out". Oxidized hemoglobin is a stronger acid than is reduced hemoglobin, and in consequence when oxygen is taken up in the lungs it provides an acid (oxyhemoglobin) to take the place of the CO_2 which escapes. Conversely, when the blood passes through the tissues and loses oxygen, the change replaces an acid (oxyhemoglobin) with a relatively neutral substance (reduced hemoglobin) and permits the blood to take up in its place an equivalent of carbonic acid without raising its hydrogen ion concentration by more than a barely measurable extent. Simultaneously with the gas changes, chlorides, carbonates and water shift between the cells and the plasma. The changes all follow definite laws, which have been tentatively formulated by Henderson, but the data for applying them in a way to place them on an accurate quantitative basis are not available. They can be made so only by the efforts of several men working simultaneously on the same blood samples, since it is necessary that all the determinations be done within the same hour on the fresh blood sample. As the study of respiratory and circulatory diseases in this Hospital affords material for direct application of the theoretical information which it is hoped to gain, and as our laboratory and Henderson's had both been engaged independently in work leading up to this problem, it seemed in every way desirable that the collaboration suggested through Doctor McLean by Professor Henderson should be

attempted. It is expected that the work will be shared by Doctors McLean, Austin, Cullen, Van Slyke, and J. P. Peters, formerly of the Cornell staff, who is entering the laboratory as a voluntary assistant.

HOMER F. SWIFT